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EDITORIAL COMMENT

Utilizing the MOGE(S) Classification for Predicting Prognosis in Dilated Cardiomyopathy*

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Cardiomyopathy is defined as a myocardial disorder of unknown origin in which the heart muscle is structurally and functionally abnormal. Little has changed from the original definition offered by Goodwin and Oakley in 1972, when they classified cardiomyopathies as dilated, hypertrophic, and restrictive (or obliterative) (1). Subsequently, the "myocardial disease of unknown origin" concept was adopted in the 1976 World Health Organization classification (2). This definition was substantially unchanged until the American Heart Association (3) in 2006 and the European Society of Cardiology (1) in 2008 formally recognized genetic and nongenetic (or acquired and mixed) forms.

Grouping cardiomyopathy into morpho-functional phenotypes, such as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy, restrictive cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy, has been key for the extraordinary progress in understanding the etiologic basis, both genetic and nongenetic, of cardiomyopathies. In day-to-day clinical practice, patients are managed exclusively according to their morpho-functional phenotype. The revelation that most cardiomyopathies are familial diseases has spurred identification of disease-causing genes, starting with linkage analysis in large families (4), and subsequently exploiting genome-wide associations (5) and next-generation sequencing up to exome and whole-genome sequencing.

Genetic testing is fast becoming part of the diagnostic evaluation of cardiomyopathies (6). The current problem: interpreting the role of mutations that are identified when screening multigene panels, especially in cardiomyopathies that do not exhibit clinical markers associated with defects of specific genes. Cardiomyopathies are genetically heterogeneous diseases; each subgroup of cardiomyopathy can be causally linked to different genes whose effects produce a similar phenotype. Consequently, gene-specific treatments are not available for cardiomyopathic disorders, with a few exceptions for phenocopies; these include storage diseases with cardiac involvement in which disease-specific intervention has become available (7). Although our knowledge of the etiology of cardiomyopathies has increased exponentially, therapeutic strategies still remain based on the morpho-functional phenotype. There is an emerging clinical need for generating large subgroups of cardiomyopathies with an identical etiological basis (caused by mutations of the same genes or the same specific mutations) to develop targeted treatments. The paradigmatic example on how the molecular and genetic mechanisms of diseases affect therapeutic innovation comes from the growing array of targeted treatments used in cancer management that have dramatically altered clinical outcomes. In cardiovascular medicine, cardiomyopathies may prove to be among the most eligible disorders amenable to targeted intervention.

In 2013, the World Heart Foundation endorsed a comprehensive classification system for cardiomyopathies called MOGE(S) (8), which maintained the morpho-functional identification but prominently addressed the disease's genetic basis. Similar to the

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3 major nosologic descriptors of TNM (tumor; nodes; metastasis) cancer staging, the MOGE(S) classification facilitates a comprehensive disease description in 5 specific categories.

- M stands for the morpho-functional phenotype of the cardiomyopathy, presenting as hypertrophic, dilated, restrictive, and arrhythmogenic phenotypes, and includes overlapping combinations.
- O denotes organ involvement. The complete information about additional extracardiac involvement allows easy recognition of syndromic patterns.
- G, for genetic transmission, is presented as autosomal dominant, autosomal recessive, X-linked, or matrilineal; nongenetic (0) or unknown/unproven origin can also be presented.
- E, for etiology, is presented as G for genetic disease (followed by the disease gene and mutation in red if pathologic, yellow if genetic variant is of unknown significance, and green for a single nucleotide polymorphism with some possible functional effects).
- S represents disease stage, including American College of Cardiology/American Heart Association stages (A to D) followed by New York Heart Association (NYHA) functional classes (I to IV).

This nomenclature allows a more coherent and homogeneous description of etiologically diverse diseases (**Figure 1**).

CAN MOGE(S) CONTRIBUTE TO PROGNOSTIC STRATIFICATION?

In this issue of the *Journal,* Hazebroek et al. (9) applied the MOGE(S) classification and assessed its prognostic value in a cohort of 213 patients with unexplained DCM. The clinical diagnostic protocol

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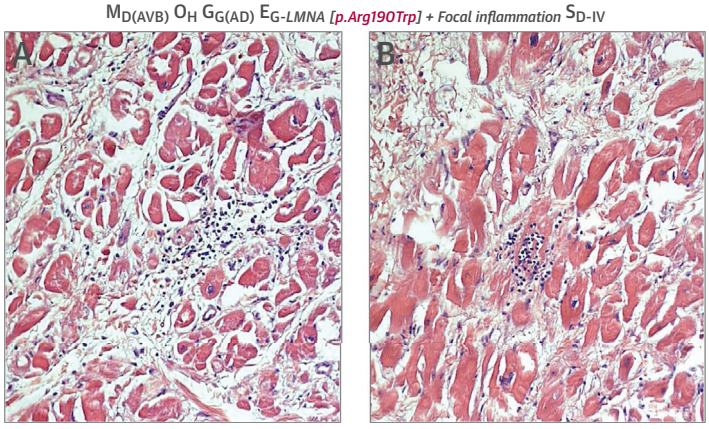
included detailed personal and family histories, physical examination, electrocardiogram, echocardiography, and right ventricular endomyocardial biopsy (EMB) for systematic determination of the deoxyribonucleic acid/ribonucleic acid profiles of 6 cardiotropic viruses. Genetic evaluation, including pedigree analysis and disease gene screening to detect pathogenic mutations, was also performed. The primary endpoints were death, heart transplantation, or life-threatening arrhythmias; the secondary endpoint focused on left ventricular reverse remodeling (LVRR) at 12 months.

The authors identified several key clinical findings from their analysis (9). At least 1 specific disease etiology was documented in 73% of the cases; more importantly, 23% of patients had >1 potential pathogenic etiology. Organ involvement outside the heart was relatively common (16%). Pathogenic mutations were relatively uncommon (8%) compared with other reported series and were understandably more commonly observed in patients with familial DCM (17%) than nonfamilial DCM (4%). Conversely, LVRR was more frequently observed in nongenetic familial DCM (40% vs. 25%). Predictors of adverse clinical outcome were higher NYHA functional class, organ involvement, and lower baseline left ventricular ejection fraction. Importantly, genetic/familial DCM alone had no prognostic significance, but when accompanied by etiological/environmental factors (i.e., significant viral load, rhythm disturbances, toxic triggers), a worse outcome was observed. The authors also developed a MOGE(S) scoring system ranging from 0 to 4, assigning 1 point for each attribute and/or gene-environment interaction (i.e., noncardiac organ involvement, gene plus environmental factors, NYHA functional class). A substantially worse outcome was observed for patients with MOGE(S) score ≥2, validating its clinical utility in a predictive model.

The strengths of the study by Hazebroek et al. (9) include the detailed systematic clinical, genetic, and pathological examinations performed in each patient;

FIGURE 1 MOGE(S) in Familial DCM

$M_{D(AVB)}$ O_H $G_{G(AD)}$ $E_{G\text{-}LMNA\ [p.Arg190Trp]\ +\ Focal\ inflammation}$ $S_{D\text{-}IV}$



The panels show 2 different pathological sections from an explanted heart: photomicrographs of a patient with familial dilated cardiomyopathy (DCM) and a pathological mutation in the *LMMA* gene. MOGE(S) describes the phenotype (D with conduction defect AVB); the heart (H) as unique organ involvement; the genetic (G), autosomal dominant (AD) transmission pattern; the etiology, genetic associated with an LMNA pathological **(red)** mutation; and stage D with New York Heart Association functional class IV.

the use of hard endpoints, including mortality and transplantation; assessment of LVRR over 1 year of complete follow-up; and the specialized expertise of a major cardiomyopathy center with established protocols for diagnosing genetic and nongenetic forms of DCM. The authors appropriately listed several of the study's limitations, including the single-center experience, the potential for selection bias (because not all patients underwent all diagnostic investigations), use of right ventricular (not biventricular) EMB with a lower rate of pathological detection of focal or multifocal myocardial processes, and the limited number of viral genomes assayed in the EMB. Furthermore, the study detected a surprisingly low percentage of pathogenetic mutations (overall 8%). In addition, cardiac magnetic resonance data, which are increasingly important in evaluating new DCM, were not provided; the study also lacked data on pharmacological therapy and its effects on left ventricular remodeling. Finally, due to the small sample size and the relatively low event rates, the study had insufficient power to perform multivariable modeling to test for independent predictors of outcome. Nonetheless, this novel study supports the idea of applying the MOGE(S) classification to assess clinical prognosis and risk stratification in patients with DCM. Although the scoring system proposed by Hazebroek et al. requires validation in a larger series, the study affirmed the need for more precise risk stratification that includes the specific etiologic basis or bases of disease.

This study (9) helps validate the important concept that a combination of etiologic factors, specifically genetic and environmental factors, might jointly participate in DCM pathogenesis. Although this is not a novel concept, the study provides insights into how to move forward with the difficult task of integrating genetics and a systematic search for contributory environmental factors.

The MOGE(S) classification of cardiomyopathies has been attracting clinical attention because of its ability to integrate comprehensive data into a single descriptor. Its importance for prognostic risk stratification could add considerably to its original descriptive and diagnostic attributes. Further studies in larger and more diverse cardiomyopathy cohorts will be necessary to validate and extend the work by Hazebroek et al. (9). Nonetheless, these intriguing findings suggest that more precise disease staging could pave the way for improving the prognosis in DCM through disease-specific therapeutic strategies. Perhaps it is time for the MOGE(S) classification to enter into more routine clinical use.

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